BARBITURATES

They are among the most useful of all drugs. In small doses they act as sedatives; in larger doses they induce sleep; in still larger doses they are able to produce deep anesthesia

by Elijah Adams

The barbiturates are the most versatile of all depressant drugs. They can produce the whole range of effects from mild sedation to deep anesthesia—and death. They are among the oldest of the modern drugs. Long before reserpine and chlorpromazine, the barbiturates were being used as tranquilizers. Indeed, phenobarbital has been called "the poor man's reserpine." Had phenobarbital been introduced five years ago instead of half a century ago, it might have evoked the same burst of popular enthusiasm as greeted Miltown and its fashionable contemporaries. Not that the vogue of the barbiturates is any less spectacular, in terms of total production and consumption. The U. S. people take an estimated three to four billion doses of these drugs per year, on prescription by their physicians. The barbiturates rank near the top of the whole pharmacopoeia in value to medicine. They are also a national problem.

It was nearly a century ago that a young assistant of the great chemist August Kekulé in Ghent made the first of these compounds. In 1864 this young man, Adolf von Baeyer, combined urea (an animal waste product) with malonic acid (derived from the acid of apples) and obtained a new synthetic which was named "barbituric acid." There are several stories about how it got this name. The least apocryphal version relates that von Baeyer and his fellow chemists went to celebrate the discovery in a tavern where the town's artillery garrison was also celebrating the day of Saint Barbara, the saint of artillerists. An artillery officer is said to have christened the new substance by amalgamating "Barbara" with "urea."

Chemists proceeded to produce a great variety of derivatives of barbituric acid. The medical value of the substances was not realized, however, until 1903, when two other luminaries of German organic chemistry, Emil Fischer and Joseph von Mering, discovered that one of the compounds, diethylbarbituric acid, was very effective in putting dogs to sleep. Von Mering, it is said, promptly proposed that the substance be called veronal, because the most peaceful place he knew on earth was the city of Verona.

Within a few months of their report, "A New Class of Sleep-Inducers," physicians in Europe and the U. S. took up the new drugs enthusiastically. More and more uses for them were discovered. Veronal (barbital) was soon followed by phenobarbital, sold under the trade name Luminal. In all, more than 2,500 barbiturates were synthesized in the next half-century, and of these some two dozen won an important place in medicine. By 1955 the production of barbiturates in the U. S. alone amounted to 864,000 pounds—more than enough to provide 10 million adults with a sleeping pill every night of the year.

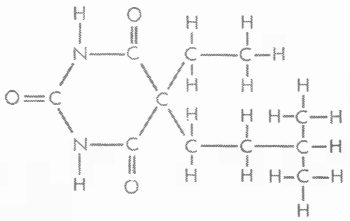
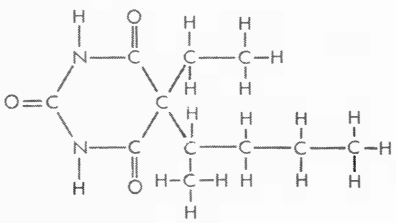
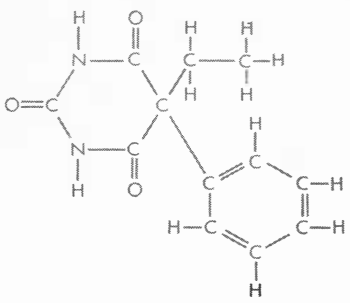
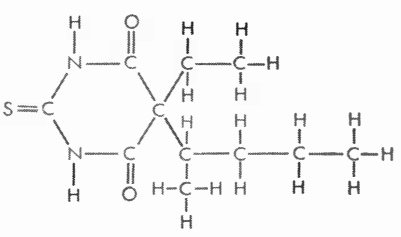
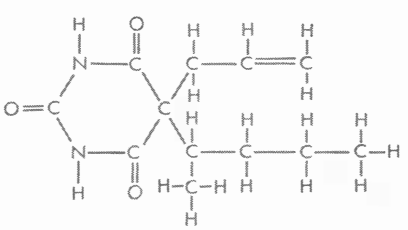
As is true of most drugs, we still do not know how the barbiturates work or exactly how their properties are related to their chemistry. The basic structure is a ring composed of four carbon atoms and two nitrogens [*see diagrams on page 64*]. Certain side chains added to the ring increase the drug's potency; in some instances the addition of a single carbon atom transforms an inactive form of the compound into an active one. Empirical analysis of the thousands of barbiturates has given us some practical information about relations between structure and activity. But by and large the mode of action of the drugs is an unsolved problem.

We know a great deal, however, about the action itself. We can follow it best by examining the successive stages of the drugs' depressant effect on the central nervous system [see "Anesthesia," by Henry K. Beecher; SCIENTIFIC AMERICAN, January, 1957]. From this standpoint the barbiturates can be considered together as a group, for the differences among them are not fundamental and concern such matters as the speed and duration of the effect.

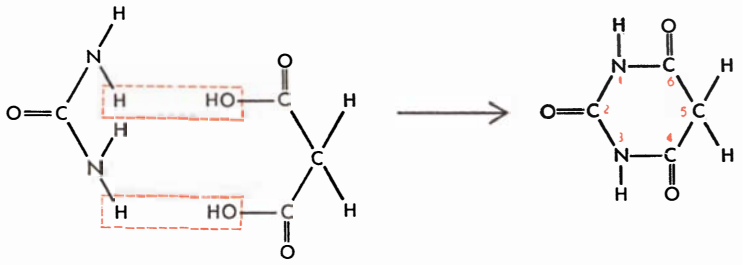
In small doses these drugs are sedatives, acting to reduce anxiety and to relieve psychogenic disorders—for example, certain types of hypertension and gastrointestinal pain. In this respect the barbiturates are yesterday's tranquilizers. They have now taken second place in popularity as sedatives to the newer tranquilizers.

At three to five times the sedative dose, the same barbiturate produces sleep. Barbiturates are still by far the most widely used drugs for this purpose, as millions of us know. Hardly any hospital patient has escaped his yellow or red capsule at evening, for it is an article of clinical faith that the patient needs chemical assistance to achieve sleep in his new environment. Another large block of users are the chronic travelers by plane and train. Finally there are the thousands of sufferers from insomnia who take the drugs habitually.

Many persons find barbiturate-induced sleep as refreshing as natural sleep. Others awake with a hangover, feeling drowsy, dizzy and suffering a headache. Tests show that, with or without symptoms, the barbiturates reduce efficiency: six to eight hours after a sleeping dose of sodium pentobarbital (Nembutal) the subjects perform below par on mental and memory tests. The various drugs act differently as sleep-

	FORMULA	NAMES	CHIEF USES	DURATION
		AMOBARBITAL (AMYTAL)	SEDATIVE HYPNOTIC	INTER-MEDIATE
		PENTOBARBITAL (NEMBUTAL)	HYPNOTIC	SHORT-ACTING
		PHENOBARBITAL (LUMINAL)	HYPNOTIC SEDATIVE ANTICONVULSANT	LONG-ACTING
		THIOPENTAL (PENTOTHAL)	ANESTHETIC	ULTRA SHORT-ACTING
		SECOBARBITAL (SECONAL)	HYPNOTIC	SHORT-ACTING

FIVE BARBITURATES are depicted at the left as they are commonly manufactured. As shown in the column of chemical structures, four of these drugs differ only in the chains of atoms attached to the carbon atom at the right side of their basic ring structure. The permutability of the basic barbiturate structure makes possible variations in speed and duration of its effect on the body.



BARBITURIC ACID (*right*), is made by combining urea (*left*) and malonic acid (*right*) with the elimination of water (*colored rectangles*). The barbiturate families arise from substitution of other substances for hydrogens at position 5 in the basic barbiturate structure.

producers. Some last for only three hours or less, others for six hours or more. The shorter-acting barbiturates (sodium pentobarbital, secobarbital) are appropriate for insomniacs who have trouble falling asleep; the longer-acting ones (barbital, phenobarbital) for people who go to sleep easily but awake after four to six hours. The latter drugs, however, are more likely to produce a hangover.

In large doses a barbiturate acts as an anesthetic. Not only does the patient become unconscious, but his spinal cord reflexes are depressed so that the muscles are relaxed and manageable for surgery. Like the gaseous anesthetics, the barbiturates depress the cerebral cortex first, then lower brain centers, next the spinal cord centers and finally the medullary centers controlling blood pressure and respiration.

The fast-acting barbiturates produce anesthesia more rapidly than ether: the patient passes from the waking state to anesthetic coma in a few moments. Sodium thiopental is the most widely used. It has important advantages over a gaseous anesthetic such as ether. Injected intravenously, it works rapidly, avoids the sense of suffocation, requires no special equipment, is free from the explosion hazard and from respiratory complications. A barbiturate anesthetic has, however, an outstanding disadvantage: the dose necessary for good muscular relaxation may seriously reduce oxygen supply to the tissues by depressing the brain center that drives respiration. Consequently for a long operation the barbiturate is often combined with a gaseous anesthetic; for a short one the dose is reduced and combined with a specific muscle-relaxing drug that has no brain-depressant action.

There are two other interesting uses of the barbiturates. One of them is in the field of psychology. As Henry Beecher observed in his article on anesthesia in SCIENTIFIC AMERICAN, an anesthetic can provide "planned access to levels of consciousness not ordinarily attainable except perhaps in dreams, in trances or in the reveries of true mystics." During World War II the barbiturates, particularly thiopental, were used for analysis and therapy for many thousands of GIs, who by this means relived and verbalized traumatic battle experiences which had been buried beyond voluntary recollection. The inhibition-relieving action of these drugs has also been employed by the police—in which application the press has given them the name of "truth serum," although they are neither a serum nor a guaranteed truth-producer.

The other important use of the drugs is for the control of epileptic convulsions. Certain of the barbiturates—phenobarbital, mephobarbital and methabarbital—can prevent or stop these seizures by depressing brain activity. Barbiturates can control not only the generalized convulsions of genuine (idiopathic) epilepsy—a disease afflicting almost a million persons in the U. S.—but also seizures induced by stimulating drugs or by bacterial toxins such as tetanus. The barbiturates and the convulsant drugs act in opposite fashion, and, curiously, each is used as an antidote for the other. Acute barbiturate poisoning is often treated with a stimulating drug such as pentylenetetrazol (Metrazol) or picrotoxin to bring the patient out of his coma; if the dose of the stimulant turns out to be too strong, producing convulsions, this in turn is treated with a dose of a fast-acting barbiturate!

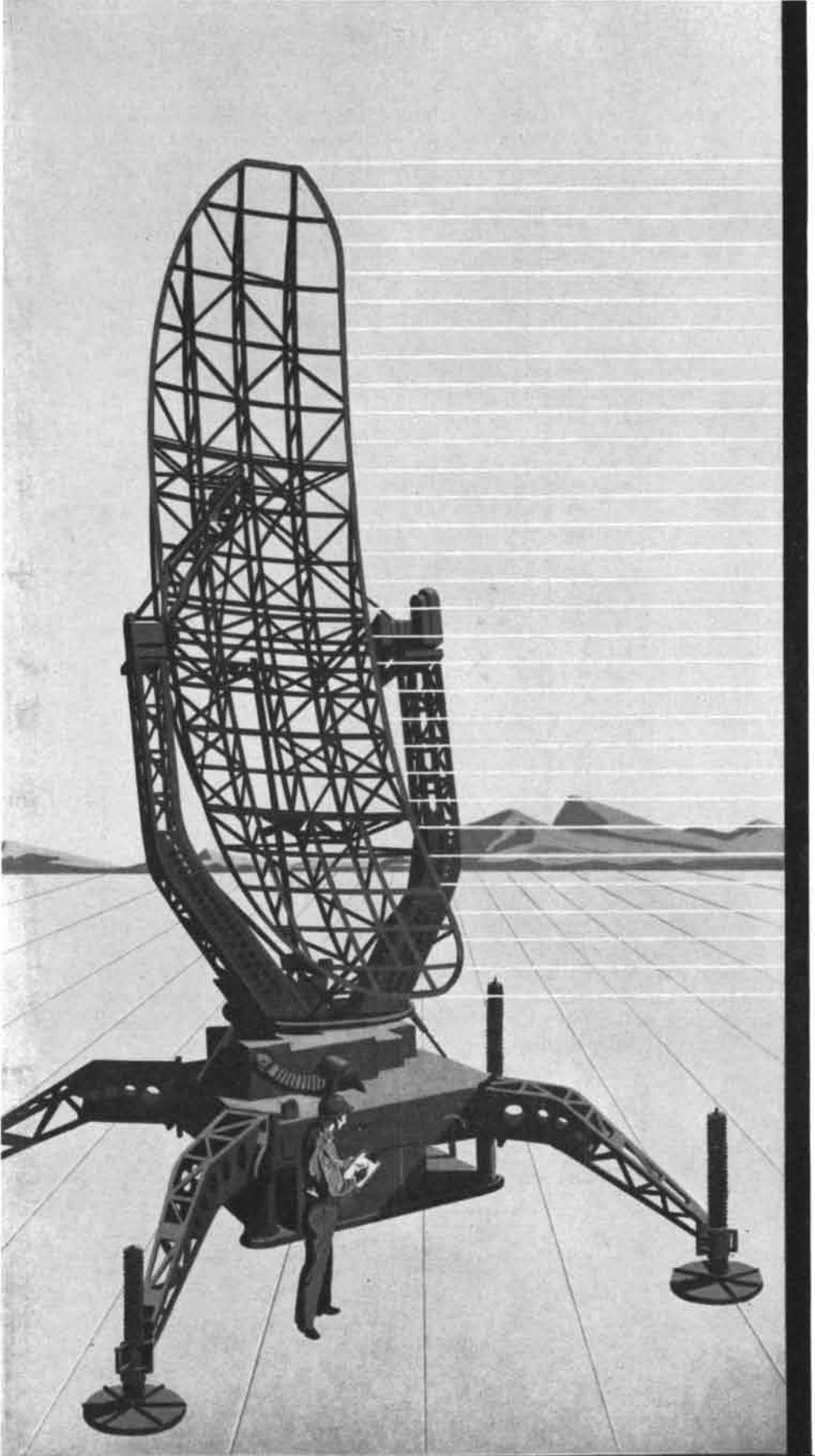
The toxic effects of barbiturates are subtle and sometimes unpredictable. For some patients even a comparatively small dose may be dangerous. The body gets rid of barbital and phenobarbital chiefly by excretion in the urine; for a person with damaged kidneys, therefore, these drugs become toxic. Pentobarbital and secobarbital, two of the most widely used barbiturates, are broken down in the liver. Given to a patient with a poorly functioning liver, they may produce a far longer sleep than desired.

Next to carbon monoxide, the barbiturates are the most popular suicide poison in the U. S. They account for one fifth of all the cases of acute drug poisoning, and most of these are suicide attempts. The barbiturates are not, as a matter of fact, a very efficient suicide agent: only about 8 per cent of those poisonees who arrive at hospitals die. But they are widely known and readily available, and they produce from 1,000 to 1,500 deaths in the U. S. each year.

Some of these deaths, though self-inflicted, are accidental. A British physician first called attention some years ago to a specific and probably common hazard. The person takes a small dose to go to sleep, and later, half asleep and confused, he swallows another, lethal dose. Some physicians now warn barbiturate-users not to keep their bottle of tablets on a night table, where they may stretch out a hand to take more while in the comatose state.

There is a comfortable margin of safety between the ordinary sleeping dose (a tenth of a gram for the average adult) and a definitely toxic dose (more than half a gram). The lethal dose is usually a gram and a half or more. Acute barbiturate poisoning has to be treated promptly. Unfortunately it is often not recognized in time, because the victim is thought to be merely in a deep sleep. The first step in treatment is to strengthen the victim's breathing, in a respirator if necessary. And a stimulant may have to be administered to restore the activity of the brain centers.

Are the barbiturates habit-forming? This much-debated question has been answered rather conclusively by recent studies. They can indeed produce addiction and chronic intoxication. The two chief criteria of addiction to a drug are a heightened tolerance to it and physical dependence on it, so that removal of the drug produces withdrawal symptoms. A morphine addict, for example, may be able to take many times the dose that would be lethal for a normal person, and he becomes acutely sick if the drug is stopped. Several years ago Havelock Fraser, Harris Isbell and their associates at the U. S. Public Health Service hospital for drug addicts in Lexington, Ky., made a thorough study of whether the barbiturates had these properties. Their investigation included experiments with human subjects who



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were given large doses of barbiturates over a period of months and then abruptly taken off the drug.

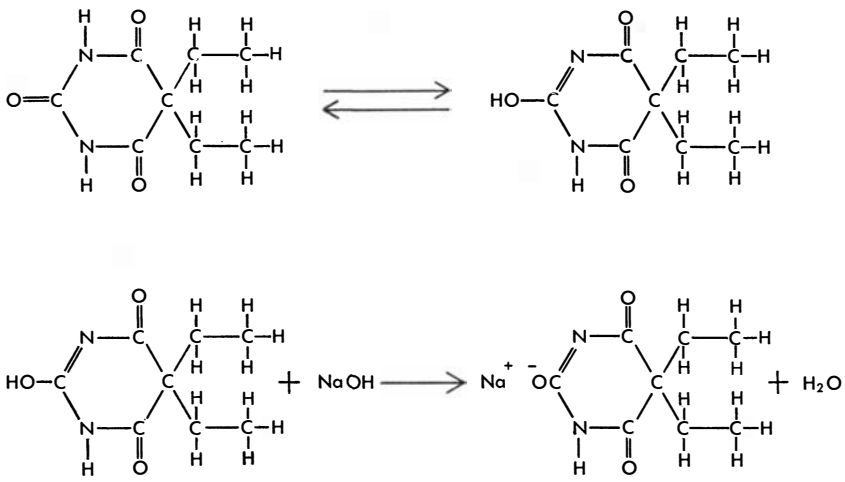
They found that the barbiturates acted as addicting drugs in every respect—physical and psychic. The men behaved like chronic alcoholics: they neglected their appearance and hygiene, became confused and quarrelsome, showed unpredictable mood swings and lost physical coordination and the mental discipline necessary for simple games. After abrupt withdrawal of the drug, the subjects began within a few hours to show signs of increasing apprehension and developed weakness, tremors, nausea and vomiting. In the next five days most of the subjects had convulsions like those of epilepsy and an acute psychosis such as alcoholics suffer, with delirium and violent hallucinations.

The Lexington investigators also made similar tests on dogs. They too exhibited withdrawal symptoms. In their "canine delirium" the dogs would stare at a blank wall and move their heads, eyes and ears as if responding to imaginary animals, people or objects; even while alone in a cage a dog would growl as if being attacked.

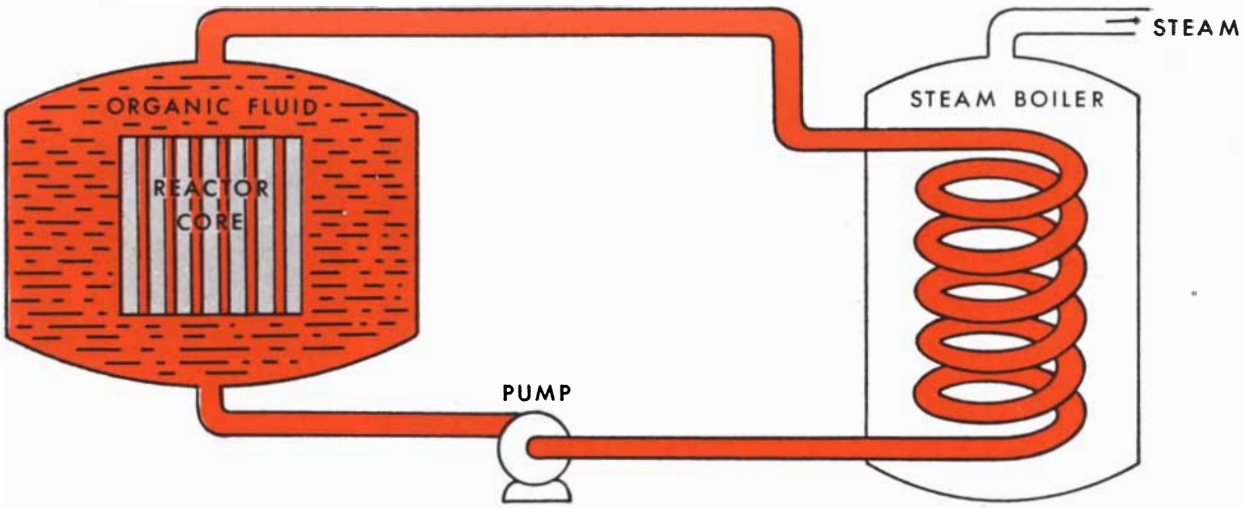
Stories in the press have greatly exaggerated the extent of barbiturate addiction in the U. S. "Thrill pills," "goof balls," "wild geronimos," "red devils" (secobarbital), "yellow jackets" (sodium pentobarbital), "blue heaven" (amobarbital)—all these terms certainly have a currency in a limited circle of addicts, but the number of addicts is not nearly so large as some of the stories have alleged. There are probably not more than 50,000 barbiturate addicts, compared with a million chronic alcoholics. Nevertheless, in view of the easy access to the barbiturates, the public does need to be alerted to their addictive property.

The saving fact is that it takes extraordinarily heavy use of these drugs to produce addiction. Subjects who have taken a fifth of a gram (twice the usual sleeping dose) every night for a year have shown no withdrawal symptoms after stopping the drug. In contrast, morphine, taken in the usual hospital doses for as short a time as 30 days, produces definite physical dependence. Moderate use of the barbiturates, in the doses prescribed by physicians, will not lead to addiction. Those who become addicts are probably, in the main, drug-users who turn to the barbiturates because they cannot get narcotics, alcoholics who seek relief from alcohol withdrawal and, in general, abnormal personalities who are addiction risks for any intoxication that will give psychic relief. Whether stricter Federal laws are needed to control misuse of the barbiturates has been a matter of considerable controversy.

Biologists look forward to the day when progress in medicine will make all present drugs, including the barbiturates, obsolete. Better understanding and treatment of the personal and social causes of anxiety should reduce our present reliance on chemical aids to tranquility and sleep. Meanwhile the barbiturates can teach us much about the functions of the brain and so help lead toward that more tranquil day.



SODIUM BARBITAL (*lower right*) can be made from barbital (*shown at top of diagram in its two forms*) by addition of sodium hydroxide (NaOH) and the elimination of water.



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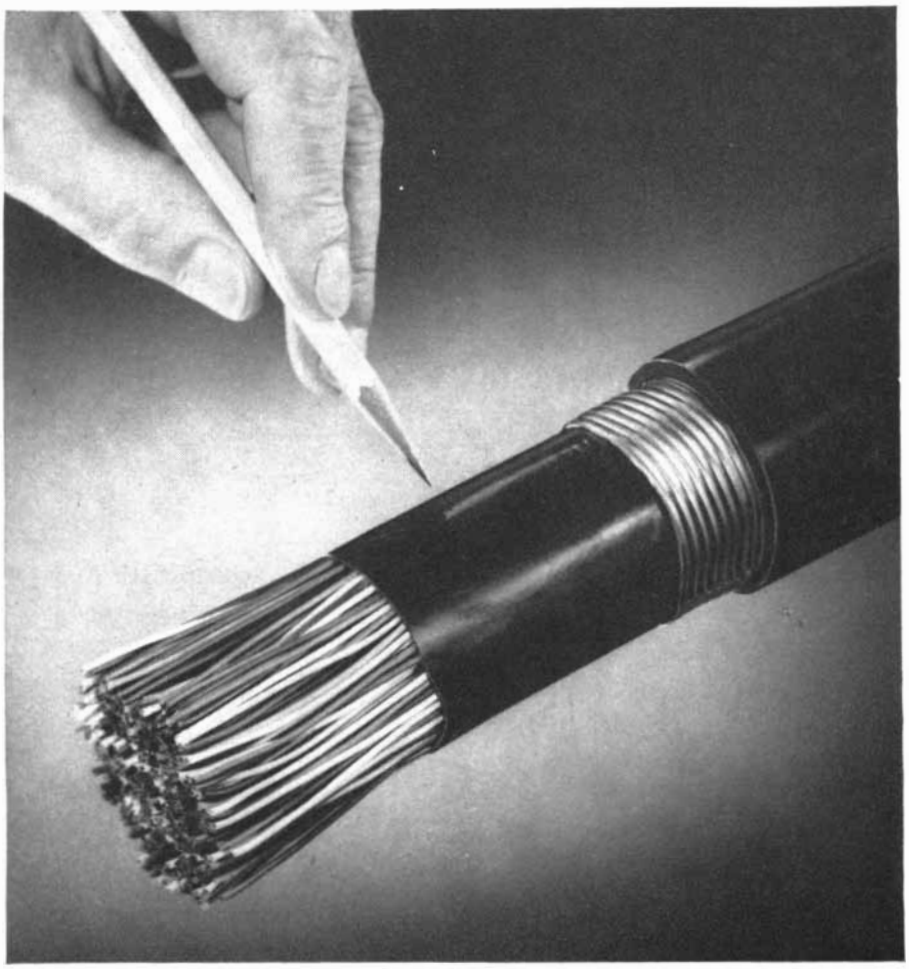

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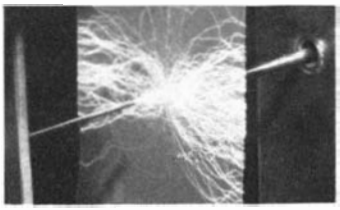

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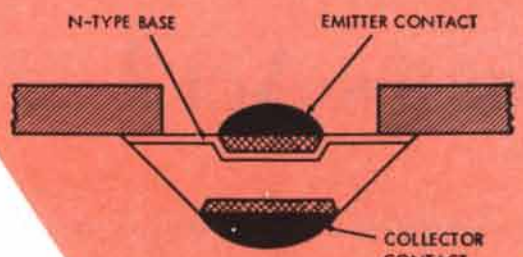

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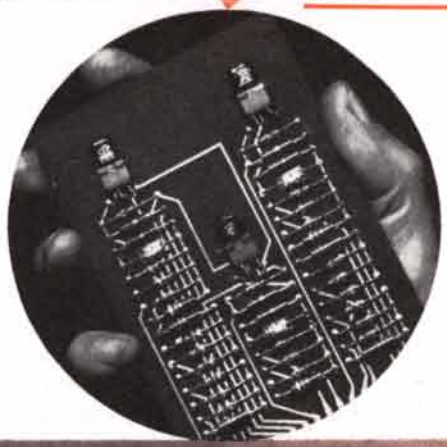

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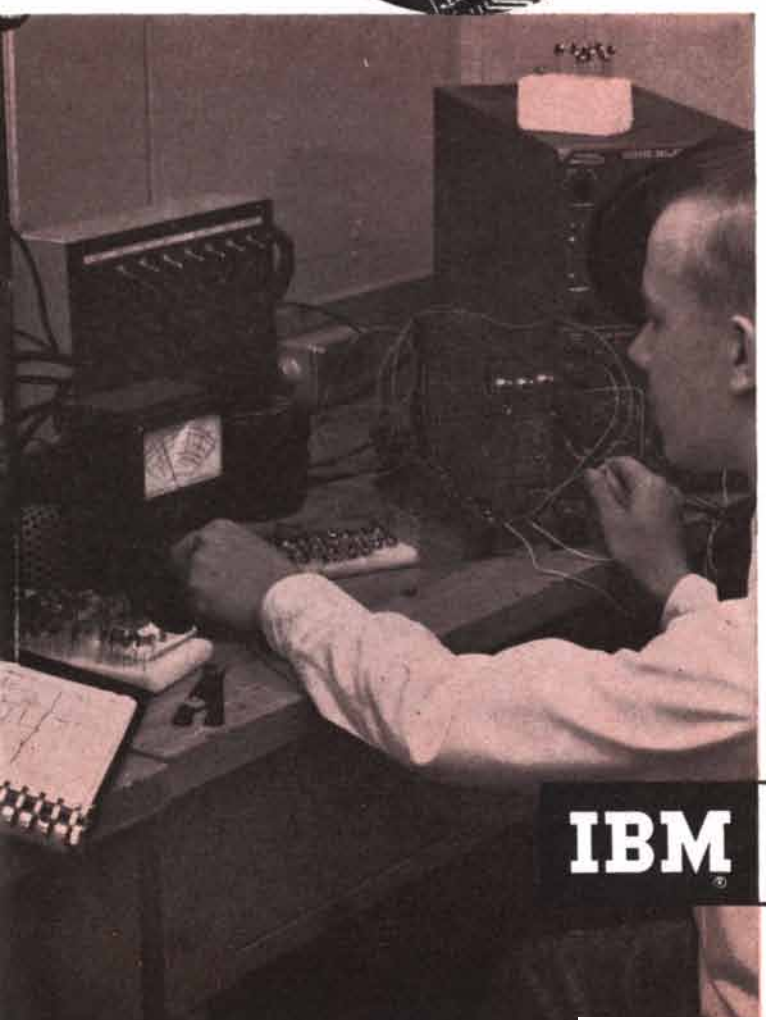

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